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Design of Highly Stable Iminophosphoranes as Recyclable Organocatalysts: Application to Asymmetric Chlorinations of Oxindoles

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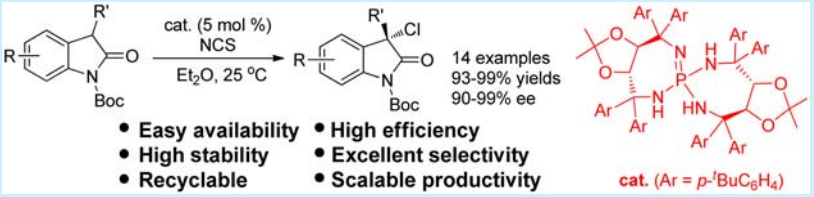
Supporting Information



ABSTRACT: A new family of tartaric acid derived chiral iminophosphoranes has been developed as highly effective organocatalysts in the asymmetric chlorinations of 3-substituted oxindoles with a high level of enantioselectivity. Importantly, these catalysts are air- and moisture-stable. Recovery of the catalyst after simple chromatographic separation for reuse in the model reaction was achieved; the catalyst can be recycled six times without loss of any enantioselectivity. Several advantages of this catalytic process are high conversion after a very short reaction time at ambient temperature, low catalytic loading, and scale-up to multigram quantities with an excellent enantiomeric excess value of >99%, which meets the enantiomeric purity required for pharmaceutical purposes.

Over recent years, chiral Brønsted base catalysis has emerged as a fast growing branch of asymmetric organocatalysis.[1] In this area, various types of single-enantiomer organobases have been developed for a wide range of catalytic enantioselective transformations.[2] Particularly, phosphorus-based nonionic bases of Schwesinger's phosphazenes or Verkade's iminophosphoranes attracted much attention.[3] A few early examples of chiral versions of iminophosphoranes were prepared for metal complexation in catalysis.[4] In 2007, the research group of Ooi pioneered the design and catalytic applications of *P*-spiro tetraaminophosphonium salts in organocatalysis.[5] Since then, the application of iminophosphoranes as organocatalysts has emerged as a useful tool for the effective introduction of chirality into target molecules.[5−8] Although these catalysts offer good enantiocontrol, there is still much room for improvement with respect to robustness, stability in air and moisture, and ease of handling.[6,9] Specifically, to bring organocatalysis into the realm of practically useful methodologies, the loss of enantioselectivity in scale up, the low turnover, and difficult catalyst recovery present great challenges to be overcome from research and industrial points of view.[10] In this context, we are interested in designing structurally rigid, chiral iminophosphoranes with a *P*-spirocyclic subunit. Within the structure of $(RN-)_3P{=}NR'$, we hypothesized that incorporation of a plurality of aryl rings could shield the basic site of the catalyst from moisture to improve the stability while maintaining the adequate ability of proton or other atom transfers to and from the basic site. As such, the chiral iminophosphoranes would be highly stable and effective for asymmetric reactions. Herein we wish to report the asymmetric chlorinations of 3-substituted oxindoles under the catalysis of these structurally unique organobases to form a carbon−chlorine bond.[11]

As shown in Scheme 1, starting from L-(+)-tartaric acid derived TADDOLs (**1**, TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol), TADDAmines **2** was readily prepared over two steps (azide substitution and reduction with $LiAlH_4$; see Supporting Information).[12] With TADDAmines **2** in hand, the construction of *P*-spirocyclic iminophosphoranes **3** was achieved by reaction of diamines with phosphorus pentachloride in good yields of 87−95% after chromatographic separation. Of note, another corresponding isomer **3h** in a contrasting configuration to **3g** was also prepared from D-(−)-tartaric acid in a similar manner.

At the outset of our studies, the newly designed molecular structures of both phosphonium salt (HCl salt of **3a**) and iminophosphorane **3a** containing one molecule of acetone were successfully determined by single-crystal X-ray diffraction analyses. As shown in Figure 1, the symmetric structure of phosphonium salt (**3a**·HCl) containing eight phenyl rings is

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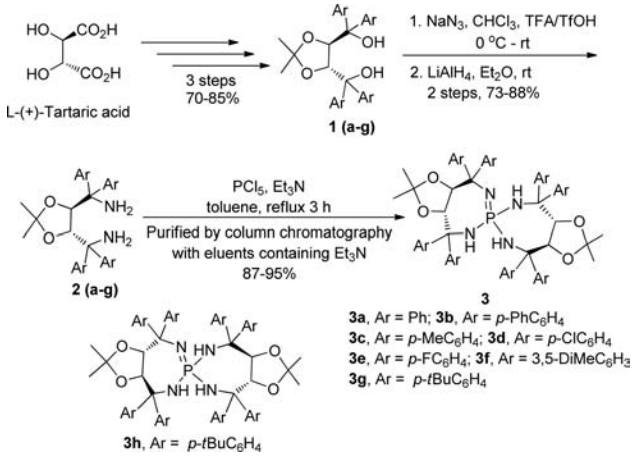
Scheme 1. Synthesis of Chiral Iminophosphoranes 3 from Tartaric Acids



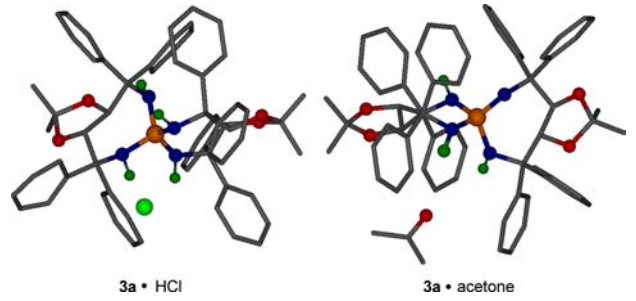
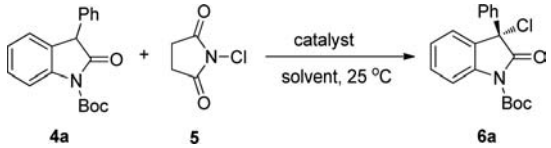


Figure 1. Single crystal X-ray structures of HCl salt of **3a** and the complex of **3a** with a molecule of acetone.

shown with a central phosphorus(V), and the chloride anion is located in proximity to two of the N–H protons with an interaction via double hydrogen bonding (atom distance of H···Cl was 2.445 Å). Interestingly, a crystallographic analysis of the acetone complex of iminophosphorane **3a** suggests the activation of the carbonyl group by double hydrogen bonding of the iminophosphorane. Both structures show that two diazaphosphacycles are linked through the phosphorus center to form a spirocycle with an encompassment of polyphenyl rings, which indicates a promising chiral environment for asymmetric induction.

With iminophosphoranes **3** in hand, we then investigated their potential as organocatalysts in the asymmetric chlorinations of 3-substituted oxindoles with *N*-chlorosuccinimide (**5**, NCS) at room temperature.[13] Table 1 shows the results from the optimization of the catalysts **3a–g** and various solvents. As can be seen, the reaction was completed within 5 min and gave the chlorinated product **3a** quantitatively in ethyl acetate as solvent. Enantiomeric excess values of 0–88% were achieved, and the catalyst **3g** furnished the best *ee* value of 88% (Table 1, entries 1–7). When the HCl salt of **3a** was used as the catalyst in this reaction, a slightly lower yield of 95% was obtained, but the enantioselectivity was greatly compromised (17% ee, Table 1, entry 8). Subsequently, in order to enhance the product *ee* value, catalyst **3a** was chosen for screening the solvents due to its easy availability. In comparison, the use of diethyl ether increases the enantioselectivity to 86% ee (Table 1, entries 9–14). Pleasingly, optimal catalyst **3g** afforded the desired product in 98% ee with a quantitative yield in diethyl ether as solvent (entry 15). An attempt to decrease the catalyst loading was

Table 1. Screening of Reaction Conditions for Asymmetric Chlorination[a]



entry	catalyst (mol %)	solvent	yield[b] (%)	ee[c] (%)
1	**3a** (10)	EtOAc	99	73
2	**3b** (10)	EtOAc	99	80
3	**3c** (10)	EtOAc	99	86
4	**3d** (10)	EtOAc	99	0
5	**3e** (10)	EtOAc	99	10
6	**3f** (10)	EtOAc	99	20
7	**3g** (10)	EtOAc	99	88
8[d]	**3a**·HCl (10)	EtOAc	95	17
9	**3a** (10)	toluene	99	70
10	**3a** (10)	DCM	99	23
11	**3a** (10)	MeCN	99	21
12	**3a** (10)	THF	99	35
13	**3a** (10)	dioxane	99	46
14	**3a** (10)	Et_2O	99	86
15	**3g** (10)	Et_2O	99	98
16[e]	**3g** (5)	Et_2O	99	98
17[e]	**3g** (2.5)	Et_2O	99	96
18[e]	**3h** (5)	Et_2O	99	−98

[a]Reaction conditions: **4a** (0.1 mmol, 1.0 equiv) and catalyst were dissolved in solvent (1 mL), and NCS (1.2 equiv) was added in once into this stirring solution; after stirring for 5 min, the reaction mixture was purified directly by silica gel column chromatography to yield product **6a**. [b]Isolated yield. [c]Enantiopurity of product was determined by HPLC analysis using a chiral column with hexane–isopropanol as solvent. [d]A premade HCl salt of **3a** was used. [e]NCS (1.2 equiv) was added in portions over 10 min into the stirring solution, followed by stirring for an additional 5 min.

tried; using a 5 mol % catalyst loading did not affect both productivity and enantiodiscrimination, but a slight decrease of enantioselectivity was observed in the presence of 2.5 mol % catalyst (entries 16–17). Moreover, catalyst **3h** was evaluated in the reaction under the optimized conditions, and a 99% yield with a 98% *ee* value of the corresponding isomer of **6a** was attained after 15 min (entry 18).

After optimizing the reaction conditions, we started to investigate the performance of catalyst **3g** in asymmetric chlorinations of 3-phenyl-oxindole on a preparative scale. Thus, the chlorination of **4a** with NCS produced **6a** in gram scale (1.24 g, 4 mmol, 99% yield, 99% ee) in 1 h using 5 mol % of catalyst (Scheme 2). Given that the chlorination reaction is very clean, after isolation of desired product **6a** with column chromatography, recovery of the catalyst **3g** by simple chromatographic separation was realized in 98% yield with polar eluents. Reuse and recycle of the catalyst in the reaction of **4a** with NCS six times on 1.6 mmol scale (500 mg) did not lose any efficiency or enantioselectivity, which proves the high stability of these iminophosphoranes. The results as shown in Scheme 2 suggested that this catalytic process could meet the main criteria of large-scale applications of organocatalysis (stability and availability of the catalyst, handling issues, recycling issues, conversion, and enantioselectivity).[10]

We further explored the substrate scope of 3-substituted oxindoles in the chlorination. As summarized in Scheme 3, all

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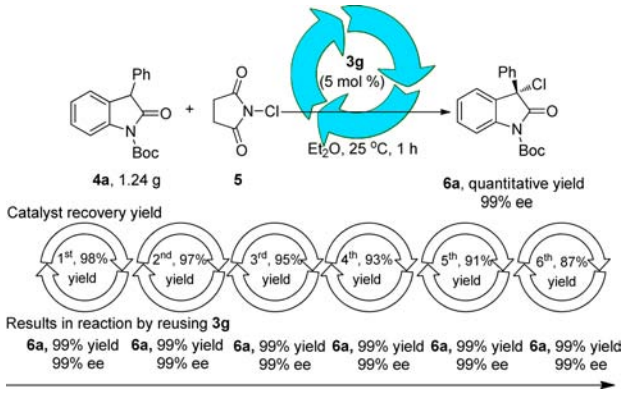
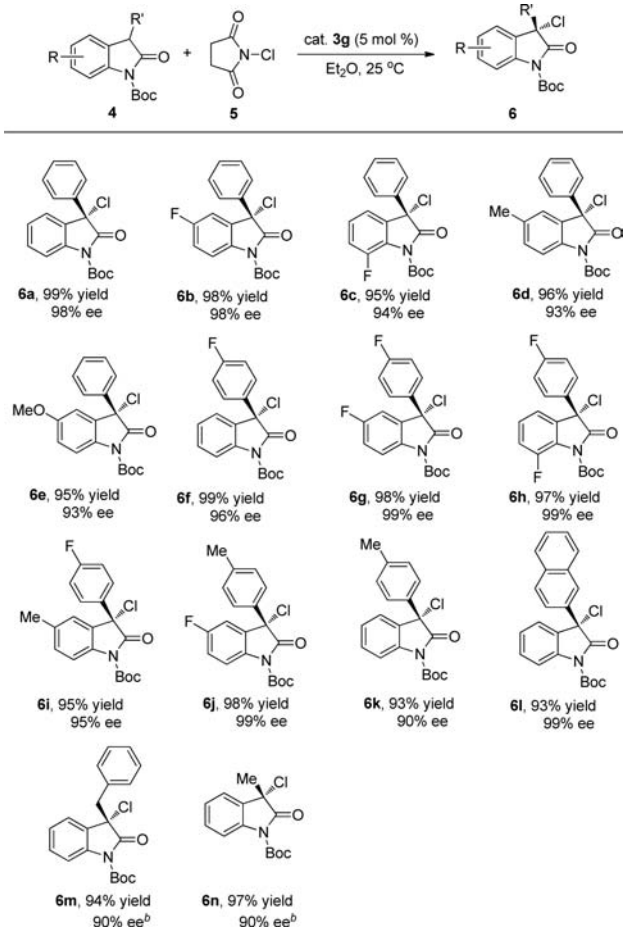
Scheme 2[a]



[a]Reaction conditions: **4a** (1.0 equiv) and catalyst **3g** (5 mol %) were dissolved in Et_2O (0.1 M), and NCS (1.2 equiv) was added in portions over 45 min into the stirring solution; after stirring for an additional 15 min, the reaction mixture was purified directly by silica gel column chromatography to yield product **6a**. Then, recovery of catalyst was performed using chromatography with hexane/EtOAc/Et_3N (10:1:1) as polar eluents.

Scheme 3. Scope of Asymmetric Chlorinations of 3-Substituted Oxindoles with NCS[a]

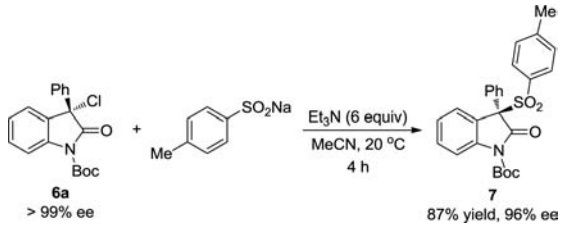


[a]All reactions were carried out with **4** (0.1 mmol, 1.0 equiv) and catalyst **3g** (0.005 mmol) in Et_2O (1 mL) at 25 °C; NCS (0.12 mmol, 1.2 equiv) was added in portions over 10 min into the stirring solution. [b]Reaction time was 1 h.

of tested 3-aryl substituted oxindoles, regardless of electron-donating or -withdrawing groups on both the oxindole core and the 3-aryl group, were converted into the corresponding products **6a–l** in high yields with excellent enantioselectivities (90–99% ee). Several cases gave the desired products with 99% ee values (Scheme 3, **6a**, **6g–h**, **6j**, and **6l**), which compare favorably with previously reported systems.[13] Notably, both high yields and excellent enantioselectivity can be obtained even with an alkyl substituent at the 3-position of the oxindole (Scheme 3, **6m** and **6n**). With a 3-benzyl substituted oxindole **4m** as substrate, the reaction affords the product with 94% yield and 90% ee after a longer reaction time of 1 h; the catalytic activity and enantioselectivity in this case are obviously superior to the results achieved by the cinchona alkaloid catalytic system in the literature (85% yield with 29% ee).[13a] In the case of 3-methyl substituted oxindole (**4n**), the chlorinated product of **6n** was furnished in 97% yield with 90% ee, which are also the best results to date in comparison to previous reports (98% yield and 62% ee achieved by using chiral calcium VAPOL phosphate;[13b] 91% yield and 22% ee achieved by using cinchona alkaloid;[13a] 86% yield and 20% ee by using a nickel(II) complex with chiral binaphthalenediimine ligands[13c]).

Intrigued by a very recent report concerning the preparation of 3-sulfonylated oxindole derivatives,[14] we employed chiral *N*-Boc protected 3-chlorooxindole **6a** as a substrate; the sulfonylation of **6a** with sodium *p*-toluenesulfinate in the presence of triethylamine as the base afforded the desired product **7** in 87% yield with 96% *ee* in acetonitrile (Scheme 4).[14]

Scheme 4. Sulfonylation of 6a for the Preparation of Chiral 3-Sulfonylated-3-Phenyled Oxindole 7



In conclusion, we have designed and developed a family of iminophosphoranes as organocatalysts. These iminophosphoranes are air- and moisture-stable, which have been applied to the asymmetric chlorinations of 3-substituted oxindoles. The desired chlorinated products were obtained in excellent yields with high levels of enantiomeric excesses (90–99% ee). Importantly, recovery of the catalyst after simple chromatographic separation for reuse in the model reaction was achieved; the catalyst can be recycled more than six times without loss of any enantioselectivity. Several advantages of this catalytic process are high conversion after a very short reaction time at ambient temperature, low catalytic loading, and scale-up to multigram quantities with an excellent enantiomeric excess value of >99%.

■ ASSOCIATED CONTENT

Supporting Information

(PDF) Crystallographic data in CIF format for the (ZDF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02323.

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Experimental details and characterization data; Experimental procedures and full spectroscopic data for all new compounds (PDF)

Crystallographic data for complex of **3a** with a molecule of acetone (CIF)

Crystallographic data for HCl salt of **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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